REMARKS

Claim 23 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for lack of an antecedent basis for the phrase "the solvent". It is respectfully submitted that this rejection is misplaced. Claim 23 depends directly from claim 22, which defines a solution which includes "a solvent". Accordingly, there is adequate antecedent basis for "solvent" in claim 22 to support a recitation thereof in dependent claim 23. Withdrawal of the rejection is requested.

Claims 19-23 and 25-32 are rejected, under 35 U.S.C. § 102(b), as being anticipated by Gierskcky et al. `412. Claims 19-35 are rejected, under 35 U.S.C. § 103(a), as being obvious over Gierskcky et al. `412 in view of Chang et al. (Journal of Photochemistry and Photobiology 1997; 28 (203): 114-22). The Applicant acknowledges and respectfully traverses the raised anticipation and obviousness rejections in view of the following remarks.

The Anticipation Rejection

The Examiner states that the claims of the present invention concern a solution comprising an "ester of 5-aminolevulinic acid at concentrations lower than 1%, not pharmaceutical nor diagnostic compositions," that the "intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art," and that "if the prior art structure is capable of performing the intended use, then it meets the claim". With regard to these three comments, the Applicants note that the claims, as amended, are clearly drawn to pharmaceutical and/or diagnostic compositions, that there is a structural difference between the presently claimed invention and the teaching of Gierskcky et al. `412, in that the present invention comprises a sub-1% solution of an ester of 5-aminolevulinic acid in a physiologically acceptable solvent, and that the compositions taught in Gierskcky et al. `412 are not capable of performing the intended use of the presently claimed compositions.

The Examiner applies Examples 1-3 (on pages 21-22) of Gierskcky et al. `412 as anticipating the presently claimed invention. However, as clearly indicated in the subtitle of each of these examples, namely, "Preparation of methyl/ethyl/n-propyl 5-aminolevulinic hydrochloride....", these examples describe the preparation (and not the product to be administered) of ALA esters at concentrations lower than 0.5% (wt/wt). It is, indeed, important to realize that these examples disclose the synthesis of ALA esters and not their administration for photodetection or phototherapeutic purposes. Presently amended and pending claim 19 does not address chemical synthesis of the product. Instead, this claim is directed at a solution to be administered to the patient for therapeutic or diagnostic purposes. Moreover, it should be noted that in the examples of Gierskcky et al. `412, excess solvents were removed by distillation giving a final concentration of 100% of dry powder. It can be readily appreciated that neither

the preparatory solutions nor the pure dry powder are appropriate for direct physiological use. For example, propyl alcohol, used in Example 3 of Gierskcky et al. `412, is known to induces haemolysis and denaturation of human erythrocytes, and is generally considered to be unsuitable for any preparation intended for internal use. Furthermore, it is commonly known to individuals skilled in the art that concentrations of this agent approaching 100% would have dramatic side effects for a patient undergoing a diagnosis or therapy procedure. Due to the known toxicity of methanol, the same deleterious results occur for solutions described in Example 1 of Gierskcky et al. `412.

With respect to Example 2, ethanol is suitable to be used in pharmaceutical formulations as long as it is only present in very low concentrations. Higher concentrations are considered strongly irritating and are thus not suitable for pharmaceutical use. Accordingly, it is respectfully submitted that solutions containing 100% of dehydrated ethanol, as described in Example 2 of Gierskcky et al. `412, are not suitable for pharmaceutical or diagnostic applications such as those of the present invention.

Finally, it should be noted that the formulations for *in vivo* administration are described in Example 7 of Gierskcky et al. `412. In this example, it is clearly indicated that 20% of the active components prepared according to Examples 1 to 3 are incorporated in a cream. Therefore, it is clear that Gierskcky et al. `412 discloses a low concentration of ALA-ester only with regard to synthesis purposes and *not* for administration to a patient. The fact that the only teaching in Gierskcky et al. `412 of a composition to be administered includes a 20% concentration of the active component (more than 2000% greater than the concentration disclosed in the present invention) serves to teach away from the present invention's use of low concentrations in such compositions.

Accordingly, by failing to anticipate all the limitations of the present claims, Gierskcky et al. `412 is insufficient to support an anticipation rejection pursuant to 35 U.S.C. § 102(b). Withdrawal of this rejection is respectfully requested.

The Obviousness Rejection

Claims 19-35 are rejected as obvious over Gierskcky et al. `412 in view of Chang et al. Chang et al. is characterized by the Examiner as disclosing "that using a specific iron chelators such as 1,2 diethyl-3-hydroxypyridine-4-one (CP94) in ALA-induced protoporphyrin IX phototherapy, reduces the skin photosensitization caused by ALA, thus allowing utilization of lower dose of ALA."

First, the Applicants would like to point out that there is a significant structural difference between ALA (disclosed in the Chang et al. reference) and its esters (employed in the present invention). This difference can be illustrated, for example, by the fact that a covalent bond

exists between the ALA molecule and the ester function. This type of bond is related to the significant difference of standard enthalpy of formation (-29.61 kcal/mol for [(CO)-(O)(H)] and -32.18 kcal/mol for [(CO)-(O)(C)]). Similarly, the disassociation mentioned by the Examiner can not be obtained simply in any aqueous solution, but requires aqueous solutions under certain conditions only, i.e., largely out of the range disclosed in the corresponding claims of the present application.

The structural difference between ALA and its esters is further accentuated by their marked difference in water solubility. This difference results in significantly different physico-chemical properties, as well as different uptake mechanisms in the organisms. In particular, it has been shown that ALA is taken up by cells through active mechanisms while ALA esters simply diffuse through cellular membranes.

The Applicants further point out that hydrolysis of the presently claimed esters into their corresponding elemental parts would result in ALA concentrations that would be unfavorable for therapeutic or diagnostic purposes.

With respect to Chang et al., this reference discloses the use of ALA at a concentration of 1% and higher. However, as stated on pages 117 and 120, increasing the concentration of ALA to 10% increases the formation of PpIX by a factor of three, and that at 1% of ALA, PpIX production was only marginal as compared to 10% concentration of ALA. Thus, it is respectfully submitted that increasing, not decreasing, the concentration of the active principle is the teaching to a person skilled in the art in order to optimize the procedure. This fact is further supported by Van den Akker et al. (attached hereto, Protochem. Photobiol. 72:681-689, 2000), who performed a standard optimization procedure of the PpIX production in vivo following exposure to ALA hexylester by increasing the concentration from 2% (no formation) to 40% (maximum formation). Thus, the fact that optimal PpIX formation is achieved using formulations according to claims 19-35 with a content of ALA esters lower than 1% is novel and surprising and not part of a standard optimization procedure.

Finally, it has been shown in vivo as well as in vitro that the proposed concentration ranges in Gierskcky et al. `412 corresponding to 40 mM to 2000 mM for ALA hexylester, will not induce any photosensitizer synthesis in tissues. In contrast, only at concentrations lower than 20 mM, corresponding to 0.5% (wt/wt), photosensitizer biosynthesis can be observed by monitoring the photosensitizer intrinsic fluorescence. In some cases, optimal photosensitizer synthesis can be observed at concentrations as low as 0.2% (wt/wt) 2 or 0.005% (wt/wt/).

If any further amendment to this application is believed necessary to advance prosecution and place this case in allowable form, the Examiner is courteously solicited to contact the undersigned representative of the Applicant to discuss the same.

In view of the above amendments and remarks, it is respectfully submitted that all of the raised rejections should be withdrawn at this time. If the Examiner disagrees with the Applicant's view concerning the withdrawal of the outstanding rejections or applicability of the Gierskcky et al. `412 in view of Chang et al/(Journal of Photochemistry and Photobiology 1997; 28 (203): 114-22) references, the Applicant respectfully requests the Examiner to indicate the specific passage or passages, or the drawing or drawings, which contain the necessary teaching, suggestion and/or disclosure required by case law. As such teaching, suggestion and/or disclosure is not present in the applied references, the raised rejection should be withdrawn at this time. Alternatively, if the Examiner is relying on his/her expertise in this field, the Applicant respectfully requests the Examiner to enter an affidavit substantiating the Examiner's position so that suitable contradictory evidence can be entered in this case by the Applicant.

In view of the foregoing, it is respectfully submitted that the raised rejection(s) should be withdrawn and this application is now placed in a condition for allowance. Action to that end, in the form of an early Notice of Allowance, is courteously solicited by the Applicant at this time.

The Applicant respectfully requests that any outstanding objection(s) or requirement(s), as to the form of this application, be held in abeyance until allowable subject matter is indicated for this case.

In the event that there are any fee deficiencies or additional fees are payable, please charge the same or credit any overpayment to our Deposit Account (Account No. 04-0213).

Respectfully submitted,

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By: _____

Print Name: Michael J. Bujold

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ANNEX 6

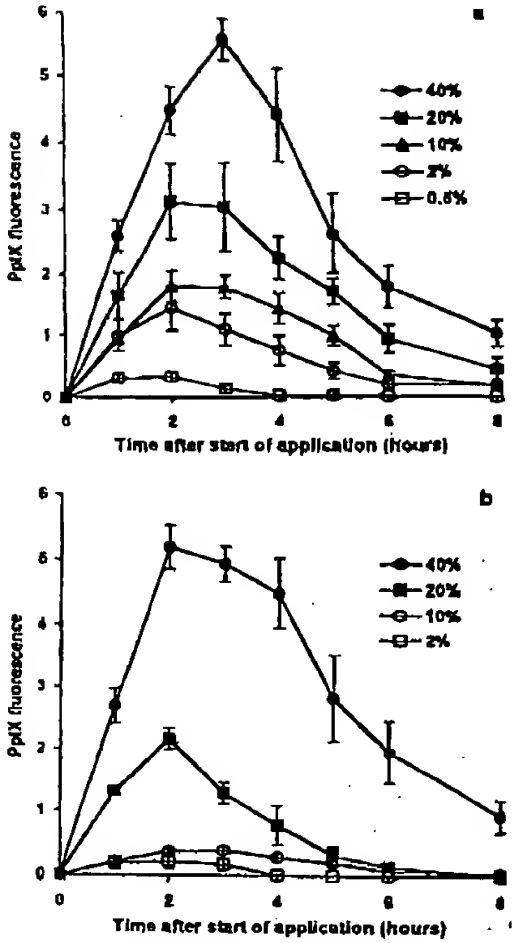

Figure 3. *In vivo* PpIX fluorescence kinetics in nude mouse skin after 10 min (a) ALA or (b) ALAHE application. The concentration of ALA or ALAHE in the cream was 0.5 (open squares), 2 (open circles), 10 (solid triangles) 20 (solid squares) or 40% (solid circles). PpIX fluorescence units are arbitrary, but comparable between all curves. Error bars indicate standard error of the mean.

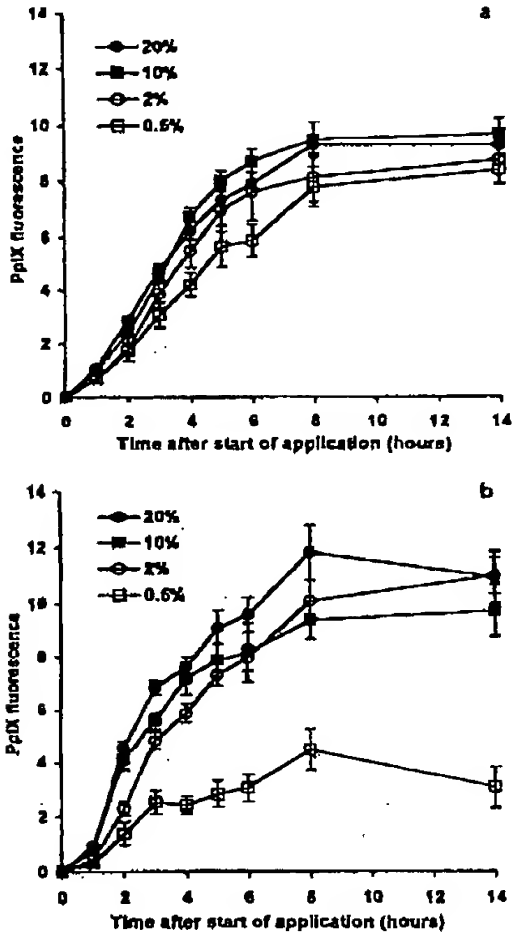

Figure 4. *In vivo* PpIX fluorescence kinetics in nude mouse skin during continuous application of (a) ALA or (b) ALAHE. The concentration of ALA or ALAHE in the cream was 0.5 (open squares), 2 (open circles), 10 (solid squares) or 20% (solid circles). PpIX fluorescence units are arbitrary but comparable among all curves. Error bars indicate standard error of the mean.

and ALAHE, possibly slightly earlier for ALAHE than for ALA.

No ALA/ALAHE ratio of the PpIX fluorescence can be calculated for the 0.5 and the 2% application concentration because the PpIX fluorescence levels are zero or too small after application of 0.5 or 2% ALAHE. Table 2 shows the ALA/ALAHE ratios of the PpIX fluorescence for 10, 20 and 40% application. The 10% ALAHE-induced PpIX fluorescence levels are small, which results in a relatively large ALA/ALAHE ratio of the PpIX fluorescence. The ALA/ALAHE ratio of the PpIX fluorescence for the 10% concentration is larger (SNK, $P < 0.01$) than the 20 and the 40% which are not significantly different from each other (SNK).

Continuous application

The PpIX fluorescence kinetics during continuous application of ALA and ALAHE up to 14 h after start of the application are shown in Fig. 4. At 24 h after start of the application, the PpIX fluorescence has decreased for all concentrations of ALA and ALAHE (data not shown). Only the 0.5% ALAHE-induced PpIX fluorescence is lower than the PpIX fluorescence after 0.5% ALA. For the other concentrations, the ALAHE-induced PpIX levels are slightly higher than the corresponding ALA-induced PpIX levels.

The ALA/ALAHE ratios are shown in Table 2 and the ALA/ALAHE ratio for 0.5% application is significantly higher than the other ratios (SNK, $P < 0.01$). The 2, 10 and 20% ALA/ALAHE ratios are the same (SNK).

Addition of penetration enhancer

Figure 5 shows that the penetration enhancer HPE-101 changes the kinetics of ALA- and ALAHE-induced PpIX. When ALA is applied for 60 min in the presence of HPE-101, the maximum fluorescence is reached at the same time point (3 h after start of application) and has the same level as with ALA application alone (Fig. 5a). However, HPE-101